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Research Highlights - 1997

Title: Preferential Formation of Benzo[a]pyrene-Diol-Epoxyde DNA Adducts at Mutational Hotspots in **p53** in Lung Cancer

Significance: In 1996, Dr. Moon-Shong (Eric) Tang and his collaborators reported the first research project ever to provide molecular evidence directly linking a cigarette carcinogen and human lung cancer. When the carcinogen benzo[a]pyrene, or BP, a component of tobacco smoke enters a human lung cell, it becomes a new carcinogenic compound called BPDE, or Benzo[a]pyrene Diol Epoxyde. The initial findings, aided by a method developed to track whether binding of the carcinogen occurs in the **p53** gene showed that the BPDE carcinogen actually binds to the **p53** gene at the exact sites where the genetic mutations are seen in this gene establishing a molecular link to lung cancer.

In a exciting subsequent study published in 1997, this research group found that most of the BPDE binding sites occur at CpG sites (i.e, sites of DNA methylation) and that the in vivo methylation of these CpG sites appears to be the underlying cause for the preferential adduct formation at these sites. This result was unexpected and has wide ramifications for the possible effects of changes in methylation patterns on patterns of DNA adduct formation by a variety of environmental carcinogens. These new data also suggest that the hotspots for mutations in the **p53** gene in lung cancers and other environmentally-linked cancers are due to carcinogen exposure. Dr. Tang's work may ultimately allow the linkage between exposure to other environmental carcinogens and mutations in the **p53** gene in other human cancers.

Reference:

- Denissenko, M.F., Pao, A., Tang, M.-s., and Pfeifer, G.P. (1996) Preferential formation of benzo[a]pyrene adduct at lung cancer mutation hotspots in **p53**. Science 274, 430-432.

- Denissenko, M. F., Chen, J. X., Tang, M.-s., and Pfeifer, G. P. (1997) Cytosine methylation determines hotspots of DNA damage in the human **p53** gene. *Proc. Natl. Acad. Sci. USA* 94, 3893-3898.

Title: Calorie Restriction: Inhibition of Carcinogenesis in an Animal Model of Genetic Susceptibility

Significance: Calorie restrictive (CR) is one of the best documented and most effective experimental manipulations for suppressing carcinogenesis (1) and extending life span (2) in rodents and in more recent reports (3). Great interest exists currently in the translation of this phenomenon to prevention strategies for human cancer, not necessarily by the direct application of CR in human populations but through the identification and manipulation of new prevention targets that are expected to emerge from a better understanding of the mechanisms underlying the antitumor effects of CR. **p53** *-/-* **mice**, in which both alleles of the **p53** tumor suppressor gene are inactivated by gene targeting, provide an attractive carcinogenesis model for cancer prevention studies, because tumor development in these **mice** is rapid and spontaneous (4) and because **p53** mutations are the most commonly observed genetic lesions in human cancer (5).

In a series of papers, including a publication this last year, Dr. Hursting and colleagues reported that CR delays spontaneous carcinogenesis in **p53** *-/-* **mice** (6), suggesting that CR modulates carcinogenesis by **p53**-independent mechanisms. In their more recent studies (7) the effect of CR on spontaneous carcinogenesis in **p53** *-/-* and **p53** *+/+* **mice** was compared to further evaluate the role of **p53** in the antitumor effects of CR. Their findings show that, although **p53** status clearly influences the rapidity with which spontaneous tumors develop, the effect of CR was similar in both genotypes, consistent with a **p53**-independent mechanism underlying the tumor suppressive effects of CR.

Reference:

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- Hursting, S.D., Perkins, S.N., Brown, C.C., Haines, D.C., and Phang, J.M. (1997) Calorie restriction induces a **p53**-independent delay of spontaneous carcinogenesis in **p53**-deficient and wild-type **mice**. *Cancer Res.* 57, 2843-2846.

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